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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/069,847	04/30/98	HAN	M 010091-035

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EXAMINER	
FREDMAN, J	
ART UNIT	**PAPER NUMBER**
1634	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/069,847	Applicant(s) Han et al
	Examiner Jeffrey Fredman	Group Art Unit 1634

☒ Responsive to communication(s) filed on *Mar 4, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *15-63* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *15, 16, 18-45, and 47-63* is/are rejected.

☒ Claim(s) *17 and 46* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3, 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Double Patenting

1. The terminal disclaimer filed March 4, 1999 complies with the requirements and therefore no obviousness type double patenting rejection will be made with regard to U.S. patent 5,763,181.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. Claims 15, 16, 18-20, 32, 35, 56, 57 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Takahashi et al (Anal. Biochem. (1991) 198:246-249).

Takahashi teaches a method of continuously detecting a specific nucleic acid sequence comprising the steps: a) obtaining a fluorescently labeled modified DNA oligonucleotide labeled throughout the sequence with an ethenoadenylic acid including at both ends where the oligonucleotide consists of a specific sequence (page 246, column 2, paragraph 3), b) contacting the oligonucleotide with an enzyme that facilitates nucleic acid cleavage (page 247, column 1, paragraph 1), c) continuously detecting the cleavage by detection of a change in fluorescence

intensity as the cleavage occurs (page 247, figure 1). Takahashi teaches the use of a number of enzymes including pancreatic DNAse I and pancreatic RNAse (page 246, column 2, paragraph 4). Takahashi expressly teaches that the equation used to measure the reaction is first order Michaelis kinetics (page 247, column 2).

4. Claims 15, 16, 19-21, 23, 25-30, 32, 37, 43, 45, 47, 51, 52, 55-57, and 59-63 are rejected under 35 U.S.C. 102(e) as being anticipated by Livak et al (U.S. Patent 5,538,848).

Livak teaches a method of continuously detecting a specific nucleic acid sequence within a nucleic acid amplification reaction comprising the steps: a) obtaining a fluorescently labeled modified DNA oligonucleotide labeled at both ends of the oligonucleotide with a fluorescence acceptor and fluorescence donor which include fluorescein and rhodamine (column 3, lines 29-47) where the fluorophores are attached by 12 carbon linkers (column 6, lines 40-62) and spaced about seven basepairs apart (column 2, lines 45-57), b) contacting the oligonucleotide with an enzyme that facilitates nucleic acid cleavage (column 3, lines 43-47), c) continuously detecting the cleavage by detection of a change in fluorescence intensity as the cleavage occurs (column 1, lines 44-51). Livak expressly teaches the use of a microplate reader (column 8, lines 10-18).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 15, 16, 19-35, 37, 39, 41, 43, 45, 47, 49, 51, 52, 55-57 and 59-63 are rejected under 35 U.S.C. 103 as being obvious over Ashiwara et al (Kokoku 5-15439, Marfch 1, 1993) in view of Livak et al (U.S. Patent 5,538,848).

Ashiwara teaches a method of detecting a specific nucleic acid sequence comprising the steps: a) obtaining a fluorescently labeled modified DNA oligonucleotide labeled at both ends of the oligonucleotide with a fluorescence acceptor and fluorescence donor which include fluorescein and rhodamine (page 4), b) contacting the oligonucleotide with an restriction enzyme that facilitates nucleic acid cleavage (page 5), c) detecting the cleavage by detection of a change in fluorescence intensity as the cleavage occurs (page 5).

Ashiwara does not teach performance of the method in a continuous fashion nor does Ashiwara teach BamHI.

Livak teaches a method of continuously detecting a specific nucleic acid sequence within a nucleic acid amplification reaction comprising the steps: a) obtaining a fluorescently labeled modified DNA oligonucleotide labeled at both ends of the oligonucleotide with a fluorescence acceptor and fluorescence donor which include fluorescein and rhodamine (column 3, lines 29-47) where the fluorophores are attached by 12 carbon linkers (column 6, lines 40-62) and spaced about seven basepairs apart (column 2, lines 45-57), b) contacting the oligonucleotide with an enzyme that facilitates nucleic acid cleavage (column 3, lines 43-47), c) continuously detecting the cleavage by detection of a change in fluorescence intensity as the cleavage occurs (column 1, lines 44-51). Livak expressly teaches the use of a microplate reader (column 8, lines 10-18).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescence detection method of Ashiwara to form a continuous reaction as taught by Livak since Livak states "In view of the above, the application of techniques for real-time monitoring of nucleic acid amplification would be facilitated by the availability of conveniently synthesized probe having efficient hybridization characteristics and distinct fluorescent characteristic in a bound double stranded state and an unbound single stranded state (column 2, line 66 to column 3, line 4)". An ordinary practitioner would have been motivated to combine these references in order to provide convenient real time monitoring of either restriction enzyme reactions or amplification reactions. With regard to BamHI, the examiner takes official notice that this was a functionally equivalent enzyme which was

commercially available prior to the applicant's filing date in such catalogs as the New England Biolab catalog.

7. Claims 15, 16, 18-33, 35-38, 40, 42, 43, 45, 47, 48, 51-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al in view of Livak and further in view of Friefelder et al (Molecular Biology (1983) Jones and Bartlett Publishers, Boston, MA, page 138) and further in view of Chow et al (Science (1992) 255:723-726).

Takahashi teaches a method of continuously detecting a specific nucleic acid sequence comprising the steps: a) obtaining a fluorescently labeled modified DNA oligonucleotide labeled throughout the sequence with an ethenoadenylic acid including at both ends where the oligonucleotide consists of a specific sequence (page 246, column 2, paragraph 3), b) contacting the oligonucleotide with an enzyme that facilitates nucleic acid cleavage (page 247, column 1, paragraph 1), c) continuously detecting the cleavage by detection of a change in fluorescence intensity as the cleavage occurs (page 247, figure 1). Takahashi teaches the use of a number of enzymes including pancreatic DNAse I and pancreatic RNAse (page 246, column 2, paragraph 4). Takahashi expressly teaches that the equation used to measure the reaction is first order Michaelis kinetics (page 247, column 2).

Livak teaches a method of continuously detecting a specific nucleic acid sequence within a nucleic acid amplification reaction comprising the steps: a) obtaining a fluorescently labeled modified DNA oligonucleotide labeled at both ends of the oligonucleotide with a fluorescence acceptor and fluorescence donor which include fluorescein and rhodamine (column 3, lines 29-47)

where the fluorophores are attached by 12 carbon linkers (column 6, lines 40-62) and spaced about seven basepairs apart (column 2, lines 45-57), b) contacting the oligonucleotide with an enzyme that facilitates nucleic acid cleavage (column 3, lines 43-47), c) continuously detecting the cleavage by detection of a change in fluorescence intensity as the cleavage occurs (column 1, lines 44-51). Livak expressly teaches the use of a microplate reader (column 8, lines 10-18).

Takahashi in view of Livak do not explicitly teach RNAse H or HIV retroviral integrase. Takahashi in view of Livak does not teach the specific differences wherein the fluorophores are on different molecules.

Freifelder et al teaches that pancreatic DNAse I and pancreatic RNAse enzymes are endonucleases, and therefore necessarily have the capacities expected of endonucleases. Freifelder also teaches that a variety of functionally equivalent nucleases can act on either ss DNA or dsDNA (page 138).

Chow teaches the use of the HIV retroviral integrase in nuclease cleavage assays as well as the use of double stranded DNA (page 725, figure 4 and column 2, paragraph 3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the continuous fluorescence detection method of Takahashi using the fluorescence labels as taught by Livak since Livak states "In view of the above, the application of techniques for real-time monitoring of nucleic acid amplification would be facilitated by the availability of conveniently synthesized probe having efficient hybridization characteristics and distinct fluorescent characteristic in a bound double stranded state and an

unbound single stranded state (column 2, line 66 to column 3, line 4)". Further, an ordinary practitioner would have been motivated to combine the method of Takahashi in view of Livak with the use of endonucleases as shown by Freifelder able to degrade either ss or dsDNA as well as integrases such as the HIV integrase as shown by Chow since Chow states "Its biological significance notwithstanding, the disintegration activity provides new approaches for studying integrase and the integration process. The disintegration activity can be used as an additional functional assay for integrase or related enzymes. The disintegration substrate has the advantage that the site of integration into target DNA is predetermined and can be manipulated (Page 725, column 2, paragraph 4)". An ordinary practitioner would have been motivated to combine the assay of Takahashi in view of Freifelder with the use of HIV integrase as taught by Chow for the expected benefits of developing new assays and new approaches to understanding integrase function and for the ability to utilize a target sequence which can be manipulated. Further an ordinary practitioner would have recognized that the assay of Takahashi would function with any functionally equivalent enzymes which functioned to reduce polynucleotides to mononucleotides, including DNAse, RNAse and HIV integrase enzymes (which releases mononucleotides upon cleavage).

8. Claims 15, 16, 18-33, 35-38, 40, 42-45, 47, 48, 51-63 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Takahashi in view of Livak and further in view of Freifelder and further in view of Chow and further in view of Walder et al (WO 89/09284).

Takahashi in view of Livak and further in view of Freifelder and further in view of Chow teach the method of claims 15, 16, 18-33, 35-38, 40, 42, 43, 45, 47, 48, 51-63 as discussed above. Takahashi in view of Livak and further in view of Freifelder and further in view of Chow do not teach the use of catalytic hybridization amplification.

Walder teach the method of catalytic hybridization amplification (figure 3, 4A and 4B).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescence detection method of Takahashi in view of Livak and further in view of Freifelder and further in view of Chow with the catalytic hybridization amplification method of Walder since Walder states "This results in a large increase in the level of sensitivity of the method compared to current diagnostic tests, all of which are based on stoichiometric hybridization reaction in which the target sequence is able to bind one, and only one, molecule of the probe (page 42, paragraph 2)". An ordinary practitioner would have been motivated to combine the method of Takahashi in view of Livak and further in view of Freifelder and further in view of Chow with the method of Walder for the expected benefit of increased sensitivity. An ordinary practitioner would have recognized that the use of the functional equivalent enzyme RNAse H would have been obvious.

Allowable Subject Matter

9. Claims 17 and 46 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The cited prior art does not teach or suggest detection of ligation by a continuous fluorescent assay.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1634

May 13, 1999